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RESEARCH ARTICLE

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Thromboembolic risks associated with paroxysmal and persistent atrial fibrillation in Asian patients: a report from the Chinese atrial fibrillation registry

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Abstract

Background: Several studies have reported on atrial fibrillation (AF) outcomes, including thromboembolism in patients with paroxysmal and non-paroxysmal AF; however the findings still remain controversial on whether risks differ between these clinical subtypes and limited data are available in Asian cohorts.

Methods: We compared the risk of thromboembolism between paroxysmal and persistent AF patients, in a large contemporary Chinese cohort study. A total of 8529 non-valvular atrial fibrillation (NVAF) patients from the Chinese Atrial Fibrillation Registry (CAFR) study were enrolled. The study subjects were divided into two groups: paroxysmal AF (PaAF, defined as AF lasting within 7 days, $n = 4642$) and persistent AF (PeAF, lasting over 7 days, $n = 3887$) groups.

Results: In non-anticoagulated patients, PeAF group demonstrated a higher risk of stroke, all-cause death, cardiac/non-cardiac death and composition of stroke/transient ischemic attack (TIA)/peripheral thromboembolism (PT)/all-cause death, compared to the PaAF group. No significant difference was found in anticoagulated subjects. On multivariate analysis in non-anticoagulated patients, age ≥ 75 years ($P = 0.046$) and prior stroke/TIA/PT ($P = 0.018$) but not AF type ($P = 0.63$) were significantly associated with the risk of stroke/TIA/PT events.

Conclusions: Stroke, all-cause death and cardiac/non-cardiac death in Chinese NVAF population was increased in non-anticoagulated PeAF patients compared with PaAF group, but same between anticoagulated PeAF and PaAF patients. After adjustment, AF type was not an independent predictor of thromboembolism in NVAF patients.

Clinical trial registration: Chinese Clinical Trial Registry ChiCTR-OCH-13003729. Registered 22 October 2013.

Keywords: Atrial fibrillation, Thromboembolism, Risk factors, Stroke, Outcome

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and is strongly associated with the risk of stroke, thromboembolism and death [1]. The risks of thromboembolism are dependent on various clinical risk factors for stroke [2]. Current guidelines recommend oral anticoagulation (OAC) in high risk patients, irrespective of whether the AF pattern is paroxysmal or

persistent [3, 4]. Nevertheless, higher AF burden and a more sustained AF pattern have been associated with a greater risk of thromboembolism [5–13], although other studies reported opposite findings [14–19]. The inconsistency may be possibly due to different sample sizes enrolled among previous studies, as well as smaller event numbers due to OAC use. Also, limited data are available from Asian population.

The Chinese Atrial Fibrillation Registry (CAFR) is a large contemporary Chinese cohort study, documenting the clinical epidemiology and outcomes in Chinese patients with AF. In this report from CAFR, we compared the risk of

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thromboembolism between paroxysmal and persistent AF patients.

Methods

The rationale and design of the CAFR study have been reported previously [20, 21]. In brief, CAFR is a prospective, multicenter, hospital-based ongoing registry conducted in Beijing, China. Ethics approval was obtained from the institutional review committee of Beijing Anzhen Hospital. Demographic data, comorbidities, treatments received and results of laboratory examinations of each patient were recorded after the patient signed the consent form. Every patient was followed up by outpatient procedures or by telephone at the time of 3 months, 6 months and every 6 months thereafter. Major events including ischemic stroke, systemic embolism and bleeding were recorded during follow-up. After excluding those who received successful radiofrequency catheter ablation therapy at baseline and during follow-up, data of 8529 NVAf patients collected between August 2011 and June 2015 were used for the present analyses.

Paroxysmal AF was defined as with spontaneous termination or with intervention within 7 days of onset, although episodes may recur with variable frequency. Persistent AF was defined as AF lasting > 7 days. Because of the sustained AF status of longstanding persistent AF and permanent AF defined in AF guidelines, the two patterns of AF were assigned to the persistent group in our study, using a simplified scheme from Levy et al. [22]. AF type of each patient was kept consistent with that of baseline regardless of later changes during follow-up.

The clinical outcomes included the occurrence of fatal and non-fatal ischemic stroke, transient ischemic attack (TIA), other non-central nervous system (CNS) peripheral thromboembolism (PT), intracranial hemorrhage, all-cause death, cardiac death, non-cardiac death and composite outcomes of stroke/TIA/PT. Endpoint events were adjudicated by neurologists according to the patients' medical records.

Baseline data of patients in different AF subtypes were reported as mean \pm standard deviation or median (25th, 75th percentiles) for continuous variables and frequencies and percentages for categorical variables. Between-group comparisons were performed using Wilcoxon rank-sum tests for continuous variables and Pearson's chi-squared tests for categorical variables.

Kaplan–Meier curves were plotted for time to clinical events in the two AF groups with or without warfarin or other oral anticoagulants in order to avoid the confounding effect of anticoagulation treatment on thromboembolism events. Cumulative incidence rates were compared with the log-rank test by groups. Multivariate Cox proportional hazards regression model was used to analyze the independent risk factors for stroke/TIA/PT [23, 24] and to assess the association between AF type and stroke risk, adjusted for AF types and components of CHA₂DS₂-VASC

score: congestive heart failure, hypertension, age \geq 75 years, age 65–74 years, diabetes mellitus, previous history of stroke/TIA/PT, vascular diseases and female gender. The proportional hazard assumption was assessed using supremum test. P value < 0.05 was regarded as statistically significant. All tests of significance were two-sided. All statistical analysis was made using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

There were 4642 patients with PaAF (54.43%) and 3887 patients with PeAF (46.88%) included for the current analysis (Table 1). Compared with PeAF patients, PaAF patients were younger, had smaller left atria (LA) diameter, and had higher creatinine clearance rate ($P < 0.001$). PeAF group had a longer history of AF and higher CHADS₂ and CHA₂DS₂-VASC scores. At baseline, PeAF patients had greater prevalence of prior history with hypertension, stroke/TIA/PT, heart failure, diabetes, myocardial infarction and peripheral artery diseases ($P < 0.001$), with no difference in history of other coronary diseases and thyroid diseases. More patients with left ventricular ejection fraction (LVEF) less than 40% were in PeAF group compared with PaAF group ($P < 0.001$). Significant higher proportions of patients with age \geq 75 years, female sex, CHADS₂ and CHA₂DS₂-VASC scores \geq 2 were observed.

Medical therapy at baseline in the two patient groups are listed in Table 1. Approximately 30% of patients with paroxysmal AF and 46.5% of patients with persistent AF were on warfarin or new oral anticoagulants (NOACs). Patients of PeAF group were more likely to be taking rate control medicines, including beta-blockers and digoxin, while PaAF group were more frequently treated with amiodarone. More patients in PeAF group were taking angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) drugs in comparison to those in PaAF group, possibly as a consequence of higher prevalence of congestive heart failure in PeAF group.

Incidence rates of thromboembolic events according to AF types were shown in Table 2, stratified by application of oral anticoagulation drugs. For AF patients not on anticoagulant therapy, the incidences of stroke/TIA/PT were 1.9 vs. 1.3 per 100 patient years for PeAF and PaAF, respectively ($P < 0.003$). Likewise, risk of all-cause death and cardiac/non-cardiac death was higher in PeAF patients.

Kaplan–Meier curves for PeAF vs. PaAF patients with or without OAC for outcomes of stroke/TIA/PT, all-cause death, cardiac death, non-cardiac death, are shown in Fig. 1. For patients not on OAC, PaAF group exhibited significantly lower HRs than PeAF group in risk of stroke/TIA/PT ($P < 0.003$), all cause death ($P < 0.0001$), cardiac death ($P < 0.0001$) and non-cardiac death ($P < 0.0001$). For patients on OAC, clinical outcomes aforementioned were

Table 1 Characteristics of patients with paroxysmal and persistent AF at study entry

Characteristics	PaAF (n = 4642)	PeAF (n = 3887)	P value
Age (y, mean \pm SD) ^a	66.8 \pm 12.12	69.1 \pm 11.23	0.000
Age group			
65–74 years, n (%) ^a	1294 (49.83%)	1078 (44.20%)	< 0.001
\geq 75 years, n (%)	1303 (50.17%)	1361 (55.80%)	
Gender, female, n(%)	2007 (43.24%)	1542 (39.67%)	< 0.001
BMI (kg/m ² , mean \pm SD)	25.1 \pm 3.69	25.4 \pm 3.69	< 0.001
SBP (mmHg, mean \pm SD)	129.2 \pm 17.17	128.6 \pm 17.76	0.114
DBP (mmHg, mean \pm SD)	76.9 \pm 10.67	78.4 \pm 11.38	0.000
LA diameter (mm, mean \pm SD)	39.1 \pm 6.72	44.9 \pm 7.09	0.000
Duration of AF history (y, mean \pm SD)	4.6 \pm 6.19	6.8 \pm 7.40	0.000
Ccr (ml/min, mean \pm SD)	78.0 \pm 33.13	74.3 \pm 33.65	< 0.001
CHADS ₂ score (mean \pm SD)	1.7 \pm 1.37	2.1 \pm 1.46	0.000
CHADS ₂ score n(%)			
0	909 (19.58%)	503 (12.94%)	< 0.001
1	1514 (32.62%)	1017 (26.16%)	
\geq 2	2219 (47.80%)	2367 (60.90%)	
CHA ₂ DS ₂ -VASc score (mean \pm SD)	2.9 \pm 1.89	3.3 \pm 1.96	0.000
CHA ₂ DS ₂ -VASc score n(%)			
0	447 (9.63%)	255 (6.56%)	< 0.001
1	764 (16.46%)	515 (13.25%)	
\geq 2	3431 (73.91%)	3117 (80.19%)	
LVEF(%, mean \pm SD)	63.0 \pm 9.31	58.9 \pm 11.29	0.000
Comorbidities n(%)			
Hypertension	3156 (68.11%)	2729 (70.35%)	0.025
Congestive heart failure	296 (6.38%)	783 (20.16%)	< 0.001
LVEF			
\geq 40%	2993 (97.27%)	2552 (92.67%)	< 0.001
0–40%	84 (2.73%)	202 (7.33%)	
Diabetes	1137 (24.49%)	1071 (27.55%)	0.001
Prior stroke/TIA/PT	819 (17.64%)	885 (22.78%)	< 0.001
Prior myocardial infarction	262 (5.65%)	259 (6.67%)	0.049
Other coronary artery diseases	815 (17.57%)	647 (16.66%)	0.269
Peripheral artery diseases	34 (1.75%)	44 (3.18%)	0.007
Thyroid diseases	153 (7.75%)	100 (7.06%)	0.452
Baseline medication n(%)			
Aspirin	2220 (47.96%)	1662 (42.86%)	< 0.001
Warfarin/NOAC	1363 (29.36%)	1808 (46.51%)	< 0.001
β -blockers	2493 (53.71%)	2291 (58.94%)	< 0.001
Digoxin	387 (8.34%)	1374 (16.11%)	< 0.001
Amiodarone	502 (10.81%)	130 (3.34%)	< 0.001
Statins	1754 (37.89%)	1551 (39.98%)	0.049
ACEI/ARBs	1705 (36.73%)	1755 (45.15%)	< 0.001

AF indicates atrial fibrillation, PaAF paroxysmal atrial fibrillation, PeAF persistent atrial fibrillation, SD standard deviation, TIA transient ischemic attack, PT peripheral thromboembolism, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LA left atria, Ccr creatinine clearance rate, LVEF left ventricular ejection fraction, NOAC new oral anticoagulation, PT peripheral thromboembolism, ACEI/ARB angiotensin converting enzyme inhibitors/angiotensin receptor blockers, CHADS₂ congestive heart failure, hypertension, age 75 years or more, diabetes mellitus and stroke, and CHA₂DS₂-VASc congestive heart failure, hypertension, age 75 years or more, diabetes mellitus, stroke, vascular disease, age 65–74 years and sex category

^aData given as n (%) or mean \pm SD

Table 2 Thromboembolic outcomes in different groups of atrial fibrillation type stratified by anticoagulant drugs during follow-up

Thromboembolic outcomes	With warfarin/NOAC		HR(95%CI)	P value ^a	Without warfarin/NOAC		HR (95%CI)	P value ^a
	Total events/n	Incidence rates/100 pt. ^a yrs			Total events/n	Incidence rates/100 pt. ^a yrs		
Stroke /TIA/PT								
PeAF	51/1804	1.2	0.988	0.955	100/2078	1.9	1.521	0.003
PaAF	37/1359	1.3	(0.647–1.509)		99/3276	1.3	(1.152–2.008)	
Stroke								
PeAF	41/1805	1.0	1.014	0.953	72/2078 77/3276	1.4	1.414	0.003
PaAF	29/1360	1.0	(0.633–1.630)			1.0	(1.025–1.950)	
TIA								
PeAF	11/1807	0.3	0.988	0.980	33/2079	0.6	2.301	0.003
PaAF	8/1362	0.3	(0.397–2.457)		21/3279	0.3	(1.331–3.977)	
PT								
PeAF	2/1808	0.0	0.470	0.408	8/3279	0.1	0.919	0.882
PaAF	3/1363	0.1	(0.078–2.814)		5/2079	0.1	(0.300–2.810)	
Intracranial hemorrhage								
PeAF	9/1808	0.2	1.806	0.875	5/2079	0.1	1.059	0.923
PaAF	6/1363	0.2	(0.386–3.054)		7/3278	0.1	(0.336–3.337)	
All-cause death								
PeAF	57/1806	1.4	1.242	0.327	201/2068	4.0	3.028	< 0.0001
PaAF	33/1361	1.2	(0.805–1.916)		104/3271	1.3	(2.389–3.836)	
Cardiac death								
PeAF	21/1807	0.5	1.603	0.237	101/2073	1.9	4.314	< 0.0001
PaAF	10/1362	0.3	(0.734–3.503)		36/3278	0.5	(2.949–6.312)	
Non-cardiac death								
PeAF	30/1808	0.7	1.17	0.599	68/2078 47/3275	1.3	2.18	< 0.0001
PaAF	18/1362	0.6	(0.652–2.099)			0.6	(1.503–3.162)	
Stroke /TIA/PT/all-cause death								
PeAF	103/1802	2.6	1.119	0.478	285/2067 191/3268	5.9	2.352	< 0.0001
PaAF	66/1357	2.4	(0.820–1.527)			2.5	(1.958–2.825)	

NOAC indicates new oral anticoagulation, HR hazard ratio, CI confidence interval, TIA transient ischemic attack, PT peripheral thromboembolism, PaAF paroxysmal atrial fibrillation, and PeAF persistent atrial fibrillation

^aIncidence rates were compared by Cox proportional hazards regression models, stratified by anticoagulant drugs

similar in PaAF as in PeAF patients ($P = 0.955$, $P = 0.327$, $P = 0.237$, $P = 0.599$, respectively).

In patients not on anticoagulation, univariate analysis demonstrates that AF type and components of CHA₂DS₂-VASc score except for the history of diabetes and female sex were associated with stroke/TIA/PT events (Table 3). On multivariate Cox proportional hazards regression models, age ≥ 75 years [HR 2.10 (1.01–4.360), $P = 0.046$] and prior stroke/TIA/PT [HR 1.86 (1.11–3.11), $P = 0.018$] but not AF type [HR 1.13 (0.69–1.86), $P = 0.63$] were independently associated with the risk of stroke/TIA/PT events.

Discussion

In this report from CAFR, our data collected from 8529 NVAf patients demonstrated that in non-anticoagulated

patients, risk of thromboembolic events was higher in PeAF than PaAF before adjusting confounders. However, this difference became not significant after adjusting age, sex, history of stroke, hypertension and vascular diseases. In contrast, in anticoagulated patients, thromboembolic risk did not differ between PaAF and PeAF before and after adjusting possible confounders.

This is one of the first comparisons of thromboembolic outcomes in different NVAf patterns in large Chinese population. As patients receiving catheter ablation treatment had a low incidence of stroke [25], we excluded those who received catheter ablation and with no AF recurrence, to avoid the dilution effect of low-risk patients. Our results strengthen the recommendation of current guidelines on stroke prevention for NVAf patients, suggesting choosing

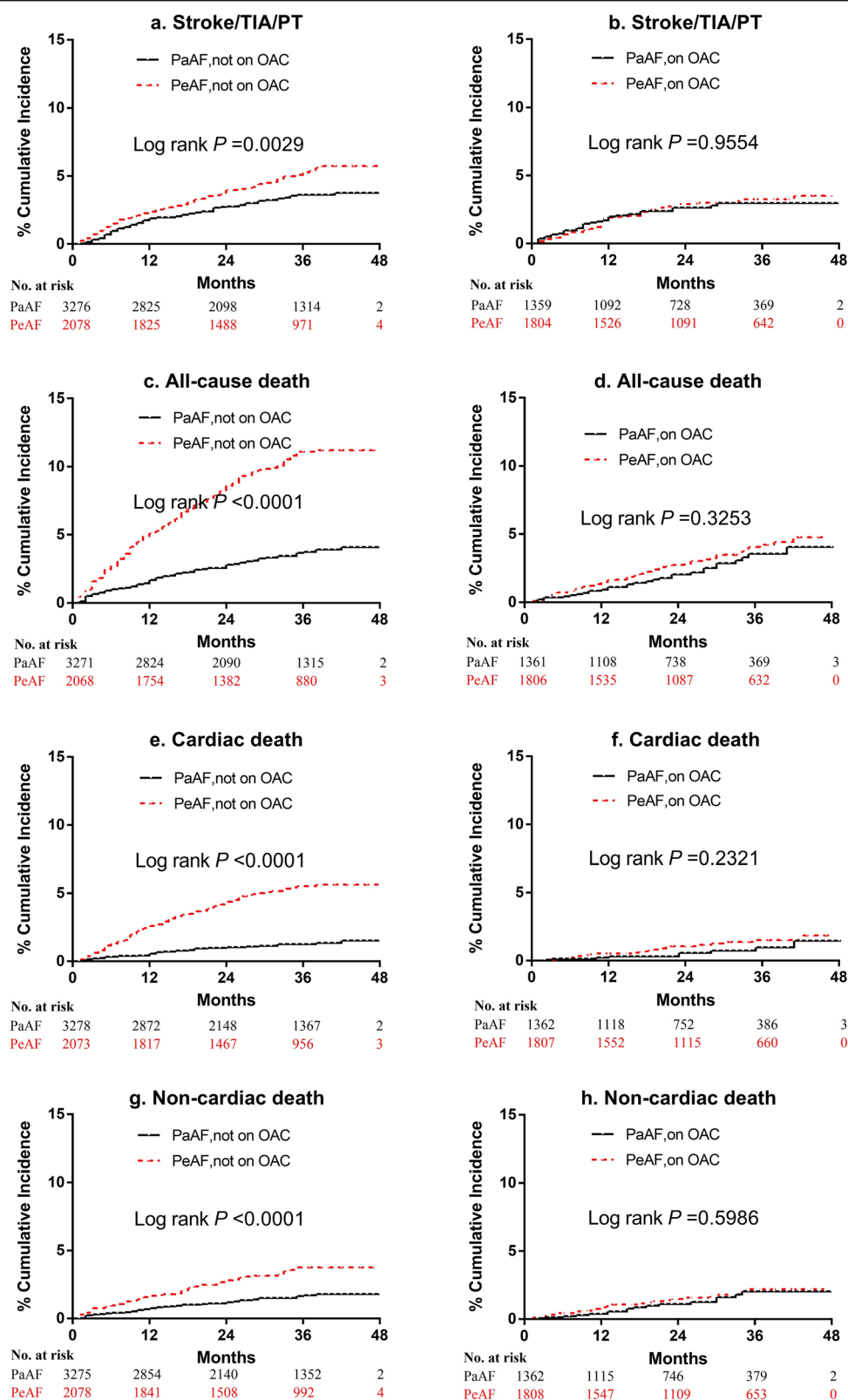


Fig. 1 Kaplan-Meier curves for occurrence of outcomes in PeAF vs. PaAF patients with or without OAC. **a, b** Stroke/TIA/PT; **c, d** all-cause death; **e, f** cardiac death; **g, h** non-cardiac death

Table 3 Univariate and multivariate analysis: stroke/TIA/PT risk factors in NVAF patients not on anticoagulants

Risk factors	Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value
PeAF vs PaAF	1.52 (1.15–2.00)	0.0031	1.13 (0.69–1.86)	0.63
Congestive heart failure	1.54 (1.09–2.17)	0.014	1.00 (0.55–1.82)	0.99
Age (≥ 75 ys)	3.56 (2.38–5.35)	< 0.0001	2.10 (1.01–4.36)	0.046
Age (65–74ys)	2.06 (1.30–3.25)	0.002	1.38 (0.62–3.08)	0.44
Hypertension	1.84 (1.30–2.61)	0.0005	1.39 (0.71–2.74)	0.34
Diabetes	1.00 (0.73–1.39)	0.996	0.82 (0.48–1.39)	0.46
Prior stroke/TIA/PT	2.51 (1.87–3.37)	< 0.0001	1.86 (1.11–3.11)	0.018
Female	1.15 (0.87–1.53)	0.31	1.44 (0.89–2.34)	0.14
Vascular diseases	2.43 (1.42–4.16)	0.001	1.54 (0.85–2.78)	0.16

TIA indicates transient ischemic attack, PT peripheral thromboembolism, NVAF non-valvular atrial fibrillation, HR hazard ratio, and CI confidence interval

anticoagulation treatment should not base on the pattern of AF.

Current guidelines recommend that the pattern of AF should not be taken into account when assessing the stroke risk and deciding the choice for thromboembolism prophylaxis treatment in patients with AF [3, 4], despite that the burden of AF is higher in PeAF patients than that in PaAF patients. Whether AF pattern is associated with stroke risk has aroused wide concern over the recent years.

Clinical trial cohorts have reported contradictory findings. A sub-analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial [14] reported a similar rate of thromboembolic events in patients with PeAF and PaAF, with a much lower incidence among the overall population (0.97%) compared with our findings. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [17], the overall risk of stroke or systemic embolism in patients with paroxysmal, persistent, and permanent AF were similar, with rates of 1.32, 1.55, and 1.49% per year, respectively. In contrast, other trials have reported different results. In the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study [13], patients with PeAF had higher adjusted rates of stroke or systemic embolism (2.18 vs. 1.73% per year, $P = 0.048$) and all-cause mortality (4.78 vs. 3.52, $P = 0.006$) compared with patients with PaAF. The same was found in SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III and V trials [11]. AF pattern was found to be an independent predictor of stroke in the sub-analysis of AVERROES (Apixaban Versus ASA to Prevent Stroke In AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) and ACTIVE A (the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trials [7], which only selected aspirin-treated NVAF patients.

Observational cohorts have also reported contradictory findings. The incidence of ischemic stroke adjusted by warfarin and other risk factors was similar in PaAF as in PeAF (2.6 vs. 2.9 per 100 patient years) from the Stockholm Cohort of Atrial Fibrillation [15]. In an Asian cohort, the crude event rate was 2-fold higher among the permanent NVAF patients (2.29%) than paroxysmal (1.16%) or persistent (1.20%) AF patients ($P = 0.001$), while after adjustment for warfarin use and risk factors, the hazard ratio for thromboembolism did not differ between paroxysmal and permanent groups [16]. In a Japanese study, Takabayashi et al. observed PaAF was independently associated with lower incidence of stroke/systemic embolism than sustained AF in patients with or without anticoagulants [8].

One of the possible reasons for the inconsistent results may be due to the use of antithrombotic therapy for preventing stroke, which will limit the outcome events and therefore, reduce the power to detect the difference of stroke incidence across AF patterns. Inconsistent anticoagulation strategy by design, imbalances of anticoagulant intensity and differences in the use of OAC rates may act as confounders. Different anti-platelet and/or anticoagulant therapy including aspirin, warfarin and new oral anticoagulants were used in various studies, with different efficacy in preventing thromboembolism. For example, the ACTIVE A and AVERROES trials [7] observed aspirin-treated NVAF patients and concluded different rates of ischemic stroke were 2.1, 3.0 and 4.2% per year for paroxysmal, persistent, and permanent AF respectively. In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial [12], in which all of the patients were treated with warfarin or NOAC, the rate of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF than paroxysmal group (1.52 vs. 0.98%, adjusted $P = 0.015$).

Of note, few studies observed thromboembolism incidence according to the stratified application of anticoagulants in different AF types. In our cohort, risk of

thromboembolic events were compared between PaAF and PeAF patients based on OAC therapy. Univariate and multivariate analysis of Cox proportional hazards regression models were performed in the absence of OAC therapy to evaluate the predictive value of AF types more accurately. For non-anticoagulated patients, PeAF group demonstrated a trend towards worse outcomes, with higher incidences of stroke/TIA/PT, all-cause death and cardiac/non-cardiac death than PaAF patients. In OAC users, risk of outcomes was comparable between PaAF and PeAF groups. Age ≥ 75 yrs. and prior history of stroke/TIA/PT were independent predictors for thromboembolism, which was consistent with most of the prior studies. The Fushimi Atrial Fibrillation Registry (The Registry Study of Atrial Fibrillation Patients in Fushimi-ku) [8] reported a lower risk of stroke/systemic embolism in PaAF patients both in non-OAC/OAC users and confirmed PaAF was an independent predictor of lower stroke/systemic embolism risk. However, our data did not find the difference, although our sample size was larger, and patients in our study had higher proportion of PaAF patients and slightly lower CHADS₂/CHA₂DS₂-VASc score.

Other reasons may possibly explain the conflicting results in different studies. For example, different risk levels of the study population are relevant. The present study showed a majority of baseline variables were evidently different between PeAF and PaAF patients, with higher risk and more underlying comorbidities in PeAF type. PaAF group had a lower CHADS₂ (PaAF vs. PeAF: 1.7 vs. 2.1, $P=0.000$) and CHA₂DS₂-VASc score (PaAF vs. PeAF 2.9 vs. 3.3, $P=0.000$), which was similar with ACTIVE-A and AVERROES [7], but lower than the results from ROCKET-AF [13] trial (mean CHADS₂ score 3.5 for both types). Our data indicated significant variations of stroke risk factors between the two types. In the presence of known risk factors involved in CHA₂DS₂-VASc score, progression from sinus rhythm to PaAF or more sustained forms is frequently seen along with atrial electrical and structural remodeling. AF types reflect different states in the process of AF progression and may be the consequence of interaction between CHA₂DS₂-VASc components rather than the risk factor of stroke.

Different proportion of PaAF patients was included in previous studies. The proportion of PaAF (54.4%) among 8529 NVAf patients in our study was similar with that of the Loire Valley Atrial Fibrillation Project (58.4%) [18], but higher than most of other studies which recruited PaAF patients less than 50%, such as ACTIVE A and AVERROES trials (24%) [7], ROCKET-AF trial (17.6%) [13], ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) Substudy (17.9%) [19], J-RHYTHM Registry (38.3%) [16] and Fushimi study (48.1%) [8]. In GISSI-AF trial [14],

higher proportion of PaAF patients (62.5%), lower CHADS₂ score (1.41 ± 0.84) and lower incidence of thromboembolic events (0.97%) were observed compared with our study. PaAF represented the early stage of AF progression, with lower AF burden than PeAF. The duration and frequency of AF episodes may have contributed to the conflicting results from prior reports.

Definitions of stroke were also different in previous trials, such as ischemic stroke (i.e. cardioembolic, atherothrombotic, or lacunar infarction) or hemorrhagic stroke, or both types. Different criteria of event ascertainment may lead to discrepancy in rate of stroke and systemic embolism. In the ARISTOTLE, Stockholm studies and Fushimi Registry [8, 12, 15], stroke endpoints were defined as a composite of ischemic and hemorrhagic stroke, while in our study and some others [14, 26], only ischemic stroke associated with AF was designed as clinical endpoints that may limit the number of events.

The event rates in our study were lower compared to that reported in other studies, despite the CHADS₂ and CHA₂DS₂-VASc scores were similar [8]. The lower incidence of thromboembolic events may be attributed to our study being a cohort reflecting current practice, with blood pressure, cholesterol and other risk factors well controlled compared to prior studies. In patients with AF and hypertension, having any elevated BP measurements was independently associated with a higher risk of stroke or systemic embolism [27]. This is supported by the post-hoc analysis of GISSI-AF trial [14], where the event rate was only 0.97% per year in patients without anticoagulants, even lower than our study. We used an independent endpoint adjudication committee to validate stroke event, which is not the usual way in observational studies and excluded about one quarter of stroke events which is self-reported by patients while turned out not to be a true event. Multiple studies have shown a progressive decline in the incidence of thromboembolism in non-anticoagulated patients identified with NVAf over the past several decades, which is evident in the present study that reports crude incident rates of $\sim 2/100$ patient years for thromboembolism. The progressive decline in thromboembolism of non-anticoagulated NVAf patients is undoubtedly multifactorial and may be secondary to improved treatment of morbidities and also by early identification of lower risk NVAf patients.

We stratified OAC use in different groups and adjusted several risk factors of thromboembolism. Some residual confoundings might still remain even after multivariate adjustment, especially factors like obesity, sleep apnea and smoking etc. Previous studies consistently indicated AF burden detected by implanted devices was associated with an increased risk of ischemic stroke [28, 29], but it is not possible for us to further stratify the PaAF patients into different levels of AF burden to investigate the differences

in risk. Future investigations are necessary to identify the correlation between AF pattern, AF burden and thromboembolic events.

Conclusions

Overall, in our large cohort of Chinese NVAf population, stroke, all-cause death and cardiac/non-cardiac death was higher in non-anticoagulated PeAF patients compared with PaAF group, but same between anticoagulated PeAF and PaAF patients. After adjustment, AF type was not an independent predictor of thromboembolism in NVAf patients.

Abbreviations

ACC: American college of cardiology; ACEI: Angiotensin converting enzyme inhibitor; AHA: American Heart Association; ARB: Angiotensin receptor inhibitor; BMI: Body mass index; CAFR: Chinese atrial fibrillation registry; CCR: Creatinine clearance; CHA₂DS₂-VASc: Congestive heart failure, hypertension, Age \geq 75 years, Diabetes, Stroke, Vascular diseases, Age 65–74 years, sex category; CHADS₂: Congestive heart failure, hypertension, Age \geq 75 years, Diabetes, stroke; CI: Confidence interval; CNS: Central nervous system; CT: Computed tomography; DBP: Diastolic blood pressure; EHRA: European heart rhythm society; ESC: Europe society of cardiology; HR: Hazard ratio; HRS: Heart Rhythm Society; LA: Left atrium; LVEF: Left ventricular ejection fraction; NOAC: New Oral anticoagulant; NVAf: Non-Valvular atrial fibrillation; OAC: Oral anticoagulant; PT: Peripheral thromboembolism; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack

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Authors' contributions

X-D and CS-M were responsible for the conception and design of the study. Y-W analyzed and interpreted the results of patients' statistic data and was a major contributor in writing the manuscript. JH-P and L-H performed data statistic analysis. GYL, J-L, GH-W, D-W and JZ-D contributed to refining the ideas and edited the manuscript. All authors contributed to critical revisions and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics approval was obtained from the institutional review committee of Beijing Anzhen Hospital. Informed consent was obtained in writing from the patients included.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Ruigomez A, Johansson S, Wallander MA, Edvardsson N, Garcia Rodriguez LA. Risk of cardiovascular and cerebrovascular events after atrial fibrillation diagnosis. *Int J Cardiol*. 2009;136(2):186–92.
- Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117(7):1230–9.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893–962.
- January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. American College of Cardiology/American Heart Association task force on practice guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1–76.
- Glutzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilkner C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2(5):474–80.
- Glutzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the atrial diagnostics ancillary study of the MDe selection trial (MOST). *Circulation*. 2003;107(12):1614–9.
- Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J*. 2015;36(5):281–287a.
- Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, et al. Incidence of stroke or systemic embolism in paroxysmal versus sustained atrial fibrillation: the Fushimi atrial fibrillation registry. *Stroke*. 2015;46(12):3354–61.
- Senoo K, Lip GY, Lane DA, Buller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. *Stroke*. 2015;46(9):2523–8.
- Scardi S, Mazzone C, Pandullo C, Goldstein D, Poletti A, Humar F. Lone atrial fibrillation: prognostic differences between paroxysmal and chronic forms after 10 years of follow-up. *Am Heart J*. 1999;137(4 Pt 1):686–91.
- Lip GY, Frison L, Grind M, Investigators S. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med*. 2008;264(1):50–61.
- Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J*. 2013;34(31):2464–71.
- Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, et al. ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF trial. *Eur Heart J*. 2015;36(5):288–296.14.
- Disertori M, Franzosi MG, Barlera S, Cosmi F, Quintarelli S, Favero C, et al. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSI-AF trial. *BMC Cardiovasc Disord*. 2013;13:28.
- Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm cohort of atrial fibrillation. *Eur Heart J*. 2010;31(8):967–75.
- Inoue H, Atarashi H, Okumura K, Yamashita T, Kumagai N, Origasa H. Thromboembolic events in paroxysmal vs. permanent non-valvular atrial fibrillation. Subanalysis of the J-RHYTHM registry. *Circ J*. 2014;78(10):2388–93.
- Flaker G, Ezekowitz M, Yusuf S, Wallentin L, Noack H, Brueckmann M, et al. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-

- LY (randomized evaluation of long-term anticoagulation therapy) study. *J Am Coll Cardiol*. 2012;59(9):854–5.
18. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, et al. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley atrial fibrillation project. *Int J Cardiol*. 2013;167(6):2682–7.
 19. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W substudy. *J Am Coll Cardiol*. 2007;50(22):2156–61.
 20. Bai Y, Bai R, Wu JH, Zhang T, Liu N, Shi XB, et al. Differences in quality of life between atrial fibrillation patients with low stroke risk treated with and without catheter ablation. *J Am Heart Assoc*. 2015;4(9):e002130.
 21. Chang SS, Dong JZ, Ma CS, Du X, Wu JH, Tang RB, et al. Current status and time trends of oral anticoagulation use among Chinese patients with Nonvalvular atrial fibrillation: the Chinese atrial fibrillation registry study. *Stroke*. 2016;47(7):1803–10.
 22. Lévy S, Camm AJ, Saksena S, Aliot E, Breithardt G, Crijns HJ, et al. International consensus on nomenclature and classification of atrial fibrillation; a collaborative project of the working group on arrhythmias and the working group on cardiac pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Europace*. 2003;5:119–22.
 23. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham study. *Am Heart J*. 1983;106(2):389–96.
 24. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF-III clinical trials. The stroke prevention in atrial fibrillation (SPAF) investigators. *Stroke*. 1999;30(6):1223–9.
 25. Hunter RJ, McCready J, Diab I, Page SP, Finlay M, Richmond L, et al. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. *Heart*. 2012;98(1):48–53. <https://doi.org/10.1136/heartjnl-2011-300720>.
 26. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke prevention in atrial fibrillation investigators. *J Am Coll Cardiol*. 2000 Jan;35(1):183–7.
 27. Rao MP, Halvorsen S, Wojdyla D, Thomas L, Alexander JH, Hylek EM, et al. Blood Pressure Control and Risk of Stroke or Systemic Embolism in Patients With Atrial Fibrillation: Results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *J Am Heart Assoc*. 2015;4(12):e002015.
 28. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (stroke preventiOn strategies based on atrial fibrillation information from implanted devices). *Eur Heart J*. 2014;35(8):508–16. <https://doi.org/10.1093/eurheartj/ehu491>.
 29. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120–9.

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